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ALKALINE HYDROLYSIS OF *p*-NITROPHENYL β-D-XYLOPYRANOSIDE

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ABSTRACT

The influence of the concentration of sodium hydroxide on the alkaline hydrolysis of *p*-nitrophenyl β-D-xylopyranoside, *p*-nitrophenyl 2-*O*-methyl-β-D-xylopyranoside, and *p*-nitrophenyl 2,3,4-tri-*O*-methyl-β-D-xylopyranoside has been investigated. Blocking of HO-2 by a methyl group results in a thousand-fold decrease of the rate. The reaction then proceeds by bimolecular, nucleophilic, aromatic substitution (S_N2Ar). The *p*-nitrophenyl β-D-xylopyranoside reaction proceeds by at least two mechanisms: an S_N2Ar mechanism, and a neighbouring-group participation of the C-2 oxyanion. Rate equations for these mechanisms have been derived. These equations show that the rate is correlated with the acidity functions H_- and J_-, and not with the stochiometric concentration of the base.

INTRODUCTION

Glycosides, as mixed full acetals, are normally stable towards bases, but certain types having a good leaving-group, such as aryl glycosides, are split by bases. Several mechanisms[1–6] are possible. The aglycon group could be released by nucleophilic attack of hydroxide (methoxide) ion, at C-1 either of the glycon group or of the phenyl ring[7]. A second mechanism[8] involves neighbouring C-2 oxyanion participation, and proceeds through a double-inversion mechanism, involving the 1,2-anhydro compound as an unstable intermediate. This intermediate then reacts rapidly either with a ring oxyanion (*e.g.*, of the primary hydroxyl group to give the 1,6-anhydride) or with the hydroxide ion of the solvent. The stereochemical requirement for operation of the anchimeric assistance is the axial disposition of the C-2 oxyanion and the C-1 phenoxyl group. This requirement is fulfilled in the β-D-xyloside *1C*(D) conformation, and thus the formation of the 1,2-anhydride, but not of the 1,6-anhydride, is possible. Furthermore, substitution of the phenyl ring with the strongly electron-withdrawing *p*-nitro group should facilitate nucleophilic aromatic substitution at the C-1 phenoxyl group. Recently, more-complex mechanisms, involving the migration[9] of the *p*-nitrophenyl group and the formation of Meisenheimer complexes[10], have been reported.

The purpose of this study was to provide some data on the kinetics of alkaline cleavage of *p*-nitrophenyl β-D-xylopyranoside, and to investigate the influence of the

concentration of the base. The alkaline cleavage of *p*-nitrophenyl 2-*O*-methyl-β-D-xylopyranoside and *p*-nitrophenyl 2,3,4-tri-*O*-methyl-β-D-xylopyranoside was also investigated. For these derivatives, anchimeric assistance by the C-2 oxyanion is prevented, and analysis of the kinetic data should be more simple.

RESULTS

p-Nitrophenyl 2,3,4-tri-O-methyl-β-D-xylopyranoside. For this derivative, the experimental pseudo-first-order rate coefficients k_1, determined at 80° and various concentrations of sodium hydroxide, are given in Table I. The possible mechanisms are an ionic mechanism[11], neighbouring C-2 methoxyl-group[11,12] participation, and a nucleophilic substitution either at C-1 of the xylose or at C-1 of the phenyl ring. However, due to the electron-withdrawing power of the nitro substituent, nucleophilic attack at C-1 of the phenyl ring[7] is more probable. The first two mechanisms are independent of the hydroxyl concentration, whereas the third one must be first order with respect to base.

TABLE I

FIRST-ORDER RATE CONSTANTS (k_1) AT 80° FOR *p*-NITROPHENYL 2,3,4-TRI-*O*-METHYL-β-D-XYLOPYRANOSIDE

NaOH (M)	H_- (25°)	K_w/h_-	$10^7 k_1$ (sec^{-1})	*log* $10^7 k_1$	
				Found	*Calc.*
0.05	12.70	0.050	6.05	0.782	0.762
0.10	12.99	0.100	11.85	1.072	1.062
0.25	13.40	0.250	26.6	1.425	1.487
0.40	13.60	0.400	53.2	1.726	1.694
0.50	13.71	0.526	60.7	1.783	1.808
0 80	13.92	0.833	106.7	2.029	2.025
1.00	14.02	1.047	129	2.114	2.129
1.50	14.20	1.585	215	2.332	2.320
2 00	14.37	2.342	330	2.519	2.491
2.50	14.54	3.472	470	2.672	2.667
3.00	14.65	4.464	603	2.780	2.781
4.00	14.95	8.928	1200	3.080	3.091

[a]From Ref. 13, p. 237.

From the data of Table I, it follows that k_1 is a linear function of the concentration of the base up to ~M sodium hydroxide. Graphical analysis shows that the function line in a plot of k_1 *versus* [NaOH] passes through the origin. Consequently, the possible contributions from an ionic mechanism or a neighbouring C-2 methoxyl-group participation must be either absent of at least very small. Calculation yields the following equation:

$$10^5 k_1\ (80°) = -0.02 + 1.31\ [\mathrm{NaOH}],$$

with standard error of the estimate $s_{y/x} = 0.03$, standard error of the slope $s_b = 0.03$, standard error of the intercept $s_a = 0.02$, correlation coefficient $r = 0.998$, and the number of points $n = 7$. The deviation of the intercept from the theoretical value zero is not statistically significant. Again, this indicates that mechanisms independent of the sodium hydroxide concentration are improbable.

For higher concentrations of the base, the linear relation between k_1 and [NaOH] no longer exists. By analogy with the acidity function (H_0) for concentrated acid solutions, acidity scales[13] for concentrated base solutions are available. The H_- scale is a measure of the ability of a strongly basic solution to abstract a proton from a weakly acidic, neutral solute molecule. Up to ~M sodium hydroxide, H_- is practically equal to 14+log [NaOH], but at higher concentrations H_- increases faster than 14+log [NaOH]. When the log k_1 values of Table I are plotted *versus* H_-, a straight line results. Calculation yields the equation:

$$\log k_1 = -19.39 + 1.04 H_-,$$

with $s_{y/x} = 0.03$, $s_b = 0.01$, $r = 0.999$, and $n = 12$. The equation was then used to recalculate the log $10^7 k_1$ values (Table I). The agreement with the experimental values is more than sufficient.

For [NaOH] = M or $H_- = 14.02$, log k_1 equals -4.89, and thus the second-order reaction constant k_2 takes the value 1.3×10^{-5} mole^{-1}.sec^{-1} at 80°. Thus, for low concentrations of sodium hydroxide, the reaction is first order with respect to the stochiometric concentration of the base, in accordance with the bimolecular substitution mechanism. For higher concentrations of sodium hydroxide, the reaction rate is correlated, not with the stochiometric concentration of the base, but with the proton-abstracting power of the solution (see below).

p-*Nitrophenyl 2-O-methyl-β-D-xylopyranoside.* The pseudo-first-order rate coefficients k_1, determined at 80°, are given in Table II. Up to M sodium hydroxide, k_1 is a linear function of the concentration of the base according to the equation

$$10^6 k_1 = -0.82 + 48.76\,\mathrm{NaOH},$$

with $s_{y/x} = 0.865$, $s_b = 1.00$, $s_a = 0.55$, $r = 0.999$, and $n = 7$.

For higher concentrations of the base, k_1 increases faster than [NaOH], but again log k_1 is a linear function of H_-. Regression analysis yields the equation

$$\log k_1 = -18.74 + 1.03 H_-,$$

with $s_{y/x} = 0.025$, $s_b = 0.01$, $r = 0.9994$, and $n = 11$.

Using this equation, log $10^6 k_1$ was recalculated and compared with the experimental values (Table II). For [NaOH] = M or $H_- = 14$, log $k_1 = -4.36$, and thus $k_2 = 4.4 \times 10^{-5}$ mole^{-1}.sec^{-1}.

In 0.5M sodium hydroxide, k_1 was determined at various temperatures, and the activation parameters were calculated (Table III). If the reaction proceeds by a bimolecular attack of the hydroxide ion on C-1 of the phenyl group, the transition state must be more ordered than the initial conformation, and thus $\Delta S^{\ddagger}$ must be

negative. Comparision of the data in Tables III and V indicates that the reason for the low rate of reaction is indeed the negative entropy difference, whereas the enthalpy factor is even more favourable than in the case of the much faster-reacting *p*-nitrophenyl β-D-xylopyranoside.

TABLE II

FIRST-ORDER RATE CONSTANTS (k_1) AT 80° FOR *p*-NITROPHENYL 2-*O*-METHYL-β-D-XYLOPYRANOSIDE

NaOH (M)	H (25°)	$10^6 k_1$ (sec^{-1})	*log* $10^6 k_1$	
			Found	*Calc.*
0.05	12.70	2.25	0.352	0.333
0.10	12.99	4.05	0.607	0.631
0.25	13.40	11.4	1.057	1.054
0.40	13.60	18.5	1.267	1.260
0.50	13.71	23.2	1.365	1.373
0.80	13.92	37.0	1.568	1.589
1.00	14.02	49.2	1.692	1.692
2.00	14.37	125	2.097	2.053
2.50	14.54	159	2.201	2.227
3.00	14.65	236	2.373	2.341
4.00	14.95	421	2.625	2.648

TABLE III

ACTIVATION PARAMETERS FOR *p*-NITROPHENYL 2-*O*-METHYL-β-D-XYLOPYRANOSIDE IN 0 5M SODIUM HYDROXIDE

t (*degrees*)	$10^6 k_1$ (sec^{-1})
70.2	8.38
75.1	14.0
80.0	23.2
84.2	35.0

$E_A = 25.0 \pm 0.2$ kcal.mole^{-1}. $\Delta S^{\ddagger}$ (60°) = −10.0 cal mole^{-1}.degree^{-1}. $\Delta G^{\ddagger} = 27.70$ kcal mole^{-1}. $\Delta H^{\ddagger} = 24.3$ kcal.mole^{-1}.

Thus, we may conclude from the dependence of the reaction rate on the concentration of the base, and from the entropy criterion, that the reaction proceeds by a bimolecular, nucleophilic attack of the hydroxide ion on C-1 of the phenyl ring. The possible contribution of an ionic mechanism or of the anchimeric assistance of MeO-2 must be either small or even absent. These conclusions are in full agreement with the results of Gasman[7]. However, at high concentrations of the base, the rate is no longer proportional to the concentration of the base, but to the proton-abstracting power of the solution. At first sight, this may seem rather unexpected since the mechanism does not involve a proton abstraction from the xyloside molecule.

Because the S_N2 reaction conforms with the generalized mechanism

$$G + HO^- \overset{K}{\rightleftharpoons} GOH^- \overset{K^\ddagger}{\rightleftharpoons} GOH^\ddagger \overset{k^\ddagger}{\rightarrow} \text{products},$$

the experimental rate constant can be calculated by the equations

$$dP/dt = K^\ddagger[GOH^\ddagger] = k^\ddagger K^\ddagger[GOH^-](f_{GOH^-}/f_{GOH^\ddagger}) =$$

$$= k^\ddagger K^\ddagger K[G][HO^-](f_G \cdot f_{OH}/f_{GOH^\ddagger}),$$

$$\text{with } K^\ddagger = \frac{[GOH^\ddagger]}{[GOH^-]} \times \frac{f_{GOH^\ddagger}}{f_{GOH^-}} \quad \text{and} \quad K = \frac{[GOH^-]}{[G][HO^-]} \times \frac{f_{GOH^-}}{f_G \cdot f_{HO^-}};$$

$$\text{experimental } k_1 = k_2[OH^-]\frac{f_G \cdot f_{HO^-}}{f_{GOH^\ddagger}}.$$

Hence, $\log k_1$ should be a linear function of the J_- acidity function[14] for the addition of hydroxide ions to an electrically neutral, indicator molecule. However, since no reliable J_- scales, based on equilibria involving hydroxide addition, are available, the kinetic J_- scale of Rochester[15] has to be used. The calculations for the 2-*O*-methylxyloside yielded the equation

$$\log k_1 = -18.86 + 1.04 J_-,$$

with $s_{y/x} = 0.05$, $s_b = 0.03$, $r = 0.998$, and $n = 11$.

Thus, $\log k_1$ is a linear function of J_-, indicating that the reaction involves the addition of a hydroxide ion to the xyloside molecule. There exists only a small difference between the equations with H_- and J_-. This is normal because, for moderate concentrations of the base, $H_- \sim J_-$. Since the H_- scale is more firmly established both theoretically and practically, we prefer to use the H_- scale, especially because the difference in temperature between k_1 (80°) and H_- and J_- (25°) is far more important than the small differences between H_- and J_-.

From the rate equation, $k_1 = k_2 A_{OH}(f_G/f_{GOH^\ddagger})$, and the equation for a Hammett base (see below, *p*-nitrophenyl β-D-xylopyranoside), $h_- = (K_w/h_-)A_{H_2O} \times (f_{B^-}/f_{HB})$, it follows that

$$k_1 = k_2(K_w/h_-)A_{H_2O}(f_{B^-} \cdot f_G/f_{HB} \cdot f_{GOH^\ddagger}).$$

It is probable that the ratios f_{B^-}/f_{HB} and $f_{GOH^\ddagger}/f_G$ are not identical, because the transition state $GOH^\ddagger$ consists of the molecule G plus an hydroxide ion. Thus, the Hammett approximation (ratio of activity functions ~ 1) will only be partially fulfilled. However, if the approximation were justified, then $k_1 = k_2(K_w/h_-)A_{H_2O}$; or even, if A_{H_2O} is taken at unity in the whole range of concentrations of sodium hydroxide, $k_1 = k_2(K_w/h_-)$.

For the 2-*O*-methylxyloside, calculation yields the equation

$$10^6 k_1 = -2.62 + 53.48\,(K_w/h_-),$$

with $s_{y/x} = 2.66$, $s_b = 0.67$, $r = 0.999$, and $n = 11$; and for the 2,3,4-tri-*O*-methyl-xyloside,

$$10^6 k_1 = -0.73 + 14.1\ (K_w/h_-),$$

with $s_{y/x} = 0.67$, $s_b = 0.31$, $r = 0.998$, and $n = 12$.

From these equations, it follows that k_1 is indeed a linear function of K_w/h_-. Because of the assumptions made, this approach is only crude, but nevertheless it yields better results than the use of the stochiometric concentrations of the base. Although it is probable that still better correlations could be found by using more sophisticated acidity functions, we feel that the lack of sufficient data (especially H_- functions at the temperature of the experiment) does not allow such further analysis.

We may conclude that the H_- or K_w/h_- functions, and not the concentration of the base, are good, but approximate, measures of the activity of the hydroxyl ion, because they take into account, at least partially, the medium effects of the solution.

TABLE IV

PSEUDO-FIRST-ORDER RATE CONSTANTS (k_1) FOR *p*-NITROPHENYL β-D-XYLOPYRANOSIDE AT 22°

NaOH (M)	$10^5 k_1$ (sec^{-1})		H_	K_w/h_-
	Found	*Calc.*		
0.01	0.025	0.022	12.00	0.010
0.02	0.052	0.044	12.30	0.020
0.05	0.105	0.106	12.70	0.050
0.10	0 211	0 206	12.99	0.100
0.20	0.388	0.388	13.30	0.200
0.50	0.854	0.864	13.71	0.526
1.00	1.54	1.406	14 02	1.047
2.00	2.47	2.290	14.37	2.342
3.00	3.44	3.300	14.65	4.464
4.00	4.69	5.013	14 95	8.928
4.94	6.65	7.160	15.14	15.0
5.93	9.36	10 24	15.36	24.0
7.91	21.6	20 0	15.74	53.0
8.89	33.8	33.2	15.96	92.0
9.68	47.9	48.7	16.10	138

p-Nitrophenyl β-D-xylopyranoside. The pseudo-first-order rate coefficients (Table IV) clearly show that the rate of the reaction is dependent on the concentration of the base, but that there is no linear relation between k_1 and [NaOH]. Furthermore, and in contrast to the *O*-methylated derivatives, $\log k_1$ is no longer a linear function of H_- or J_-. This seems rather normal, since now two reaction pathways are possible: the S_N2Ar mechanism and the mechanism involving C-2 oxyanion participation (S_Ni). Both mechanisms are dependent on the base concentration, but in a different way. According to Lai[8], the anchimeric reaction can be represented by the

following equations:

$$G + HO^- \overset{K}{\rightleftharpoons} G^- + H_2O \text{ (fast equilibrium), and}$$

$$G^- \overset{k}{\rightarrow} \text{reaction products (rate limiting),}$$

where G is the glycoside and G^- is the anionic intermediate. For phenyl β-D-xylopyranosides, G^- stands for a glycon group having an ionized hydroxyl function at C-2, and with the *trans*-diaxal conformation [*1C*(D)] required for neighbouring-group participation. Thus, the constant K is an overall equilibrium constant for deprotonation and for conformational change. The second reaction step (reaction constant k) involves heterolysis of the carbon–oxygen (exocyclic) bond with formation of a reactive intermediate (possibly, 1,2-anhydroxylose) which then reacts rapidly with the solvent HO^-. The heterolysis step is rate-limiting and independent of the base concentration. According to Lai, the rate of appearance of the nitrophenoxide ion (P) will be given by the equation

$$\frac{dP}{dt} = \frac{kK[HO^-][G_i - P]}{1 + K[HO^-]} = k_1[G_i - P],$$

with $k_1 = \dfrac{kK[HO^-]}{1 + K[HO^-]}$, and G_i = initial concentration of the xyloside.

Initially, the rate will increase with increasing concentration of the hydroxyl ion but, at higher concentrations, it will level off to a constant value ($k_1 = k$).

However, if the reaction also proceeds through the S_N2Ar mechanism, the rate will be given by the equation

$$\frac{dP}{dt} = k_2[G_i - P][HO^-] + \frac{kK[HO^-][G_i - P]}{1 + K[HO^-]},$$

where k_2 is the rate constant for the S_N2 reaction. In each experiment, $[HO^-]$ will remain almost constant and the reaction will be pseudo-first-order, but with a complex, pseudo-first-order (k_1) rate coefficient. The exact meaning of k_1 will be dependent on the concentration of the base. At sufficiently high concentrations of $[HO^-]$, $K[HO^-] \gg 1$ and the equation simplifies to

$$dP/dt = k_2[G_i - P][HO^-] + k[G_i - P] = (k_2[HO^-] + k)[G_i - P].$$

The experimental constant k_1 will still be a linear function of $[HO^-]$, $k_1 = k + k_2[HO^-]$, and no levelling off will be observed. At very low concentrations of the base, $1 \gg K[OH]$ and the equation simplifies to

$$dP/dt = k_2[G_i - P][HO^-] + kK[G_i - P][HO^-] = (k_2 + kK)[G_i - P][HO^-],$$

and $k_1 = (k_2 + kK)[HO^-]$. At intermediate concentrations of the base, no simpli-

fication is possible and

$$k_1 = k_2[HO^-] + \frac{kK[HO^-]}{1+K[HO^-]}. \qquad 1$$

However, although at high and low concentrations of sodium hydroxide the experimental k_1 was indeed a linear function of $[HO^-]$, at intermediate concentrations the experimental k_1 values could not be fitted to equation 1. By analogy with the former cases, and since the equilibrium reaction involves a proton abstraction from a weak acid, we tried to correlate the rate and the experimental k_1 with H_- and/or K_w/h_-. This could be done in the following way.

For a Hammett indicator base system (HB/B^-), the definition of H_- is given by the equations (A is the activity, and f is the activity coefficient):

$$H_- = -\log h_- = -\log A_{H^+}(f_{B^-}/f_{HB}) = pK_{HB} - \log [HB]/[B]$$

and thus,

$$h_- = A_{H^+}(f_{B^-}/f_{HB}). \qquad 2$$

For the dissociation of water, $K_w = A_{H^+} \times [HO^-] \times f_{HO^-}/A_{H_2O}$
or

$$A_{H^+} = K_w A_{H_2O}/[HO^-]f_{HO^-}. \qquad 3$$

Combination of equations *2* and *3* yields equation *4*:

$$h_- = \frac{K_w A_{H_2O}}{[HO^-]f_{HO^-}} \times \frac{f_{B^-}}{f_{HB}}, \quad \text{and} \quad \frac{A_{HO^-}}{A_{H_2O}} = \frac{K_w}{h_-} \times \frac{f_{B^-}}{f_{HB}}. \qquad 4$$

For the S_Ni mechanism, the minimum scheme will give the equations:

$$v = dP/dt = k[G^-] = kK[G]\frac{f_G A_{HO^-}}{f_{G^-} A_{H_2O}}, \quad \text{with} \quad K = \frac{[G^-]f_{G^-} A_{H_2O}}{[G]f_G A_{HO^-}}.$$

In each experiment, $f_G/(f_{G^-} \times A_{H_2O}) = \text{constant}$, and thus,
with $K' = (K.f_G)/(f_{G^-} \times A_{H_2O})$, $v = kK'[G]A_{HO^-}$.

Using Lai's approach[8], but replacing K by K' and $[HO^-]$ by A_{HO^-}, one calculates:

$$k_1 = \frac{kK' A_{HO^-}}{1+K' A_{HO^-}} = \frac{kK\frac{f_G}{f_{G^-}}\frac{A_{HO^-}}{A_{H_2O}}}{1+K\frac{f_G}{f_{G^-}}\frac{A_{HO^-}}{A_{H_2O}}}. \qquad 5$$

Substitution of equation *4* in *5* yields

$$k_1 = \frac{(kKf_G K_w f_{B^-})/(f_{G^-} h_- f_{HB})}{1+K\frac{f_G}{f_{G^-}}\frac{f_{B^-}}{f_{HB}}\frac{K_w}{h_-}}. \qquad 6$$

On the basis of the Zucker–Hammett approximation.

$$\frac{f_G}{f_{G-}} \times \frac{f_{B-}}{f_{HB}} \sim 1, \quad \text{and} \quad \text{equation } 6 \text{ simplifies to } k_1 = \frac{kK(K_w/h_-)}{1+K(K_w/H_-)}.$$

The equation for the sum of the two reactions (S_Ni and S_N2Ar) thus becomes

$$k_1 = k_2(K_w/h_-) + \frac{kK(K_w/h_-)}{1+(K_w/h_-)K}.$$

Thus, the form of the equation 1 does not change, but the concentration of $[HO^-]$ is now replaced by K_w/h_-, which is a measure of the proton-abstracting power of the solution. In our calculations, we used $K_w = 10^{-14}$ and the H_- (25°) values of Yagil[16] for aqueous sodium hydroxide. Since H_- values at higher temperatures are not available, we had to use the same K_w/h_- values (Tables I and IV) even if the rate coefficients were determined at 80°.

At high concentrations of sodium hydroxide, $K_w/h_- \gg 1$ and equation 7 simplifies to $k_1 = k + k_2[K_w/h_-]$. Graphical analysis shows that k_1 is an approximately linear function of K_w/h_- in the range 4M to 9.7M sodium hydroxide. Calculation yields the equation

$$10^5 k_1 = 1.95 + 0.333(K_w/h_-),$$

with $s_y/_x = 1.08$, $s_b = 0.01$, $s_a = 0.69$, and $r = 0.998$.

Assuming $k_2 = 0.34 \times 10^{-5}$, $k_1 - k_2(K_w/h_-)$ can be calculated for each concentration of the base, and from the equation

$$k_1 - k_2(K_w/h_-) = \frac{kK(K_w/h_-)}{1+K(K_w/h_-)}$$

the rectangular hyperbole (and k and K) can be calculated by the iterative procedure of Wilkinson[17]: $k = 2 \times 10^{-5}$ sec^{-1} and $K \sim 1$M^{-1}. These provisional values were then used in a iterative computer programme, designed to compute the most probable values of k, k_2, and K, namely, $k = 2.7 \times 10^{-5}$ sec^{-1}, $k_2 = 0.336 \times 10^{-5}$ mole^{-1}.sec^{-1}, and K (association) $= 0.82$M^{-1}.

These rate coefficients were then used to recalculate k_1 from equation 7. As can be seen from the data in Table IV, the calculated and experimental values agree. The pseudo-first-order rate coefficient k_1 was determined at various temperatures in 0.05M and M sodium hydroxide, respectively (Table V). Although the reaction proceeds by at least two different mechanisms, the experimental $\log k_1$ was a linear function of 1/T and apparent activation parameters could be calculated in the usual way. At both concentrations of the base, the apparent Arrhenius activation energy is a complex function of at least three energy differences, namely, the equilibrium $\Delta H°$, and the activation energies of the S_N2Ar (E_2) and S_Ni (E_i) reaction. The same will be

true for $\Delta H^{\ddagger}$, $\Delta G,^{\ddagger}$ and $\Delta S^{\ddagger}$. In M sodium hydroxide,

$$k_1 = Ae^{-E_2/RT} + \frac{Be^{-E_1/RT} \times e^{-\Delta H/RT}}{1+e^{-\Delta H/RT}},$$

and in 0.05M sodium hydroxide, if it is assumed that $K[OH] \ll 1$, $k_1 \sim k_2[OH] + kK[OH]$.

Hence, even in the most simple case, the experimental activation parameters have no simple meaning and exact information about the individual reaction steps cannot be gained. Considering the values of k_2 and k, it seems illogical to assume that the above equations can be simplified to expressions containing only one term. Consequently, we believe that the linearity of the plots of log k_1 versus 1/T is purely fortuitous.

TABLE V

ACTIVATION PARAMETERS FOR *p*-NITROPHENYL β-D-XYLOPYRANOSIDE

0.05M NaOH		*M NaOH*	
t (*degrees*)	$10^6 k_1$ (sec^{-1})	t (*degrees*)	$10^5 k_1$ (sec^{-1})
30.3	4.10	40.0	3.01
35.6	8.81	44.8	5.74
40.8	18.2	50.0	8.50
45.2	31.2	55.0	11.07
50.7	64.6	60.0	13.77
E_A = 26.4±0.2 kcal.mole^{-1}		E_A = 25.6±0.2 kcal.mole^{-1}	
$\Delta S^{\ddagger}$ (60°) = +7.5 cal.mole^{-1}.degree^{-1}		$\Delta S^{\ddagger}$ (60°) = +3 9 cal.mole^{-1}.degree^{-1}	
$\Delta G^{\ddagger}$ = 23.3 kcal.mole^{-1}		$\Delta G^{\ddagger}$ = 23.6 kcal.mole^{-1}	
$\Delta H^{\ddagger}$ = 25.7 kcal.mole^{-1}		$\Delta H^{\ddagger}$ = 24 9 kcal.mole^{-1}	

However, since the $\Delta S^{\ddagger}$ for the S_N2Ar reaction must be negative, the overall positive $\Delta S^{\ddagger}$ indicates that the S_Ni mechanism proceeds with a relatively high increase of the entropy. This suggests that there is a large amount of bond-stretching in the S_Ni transition state.

CONCLUSIONS

p-Nitrophenyl β-D-xylopyranoside in basic solution reacts by at least two processes. The first involves a fast, equilibrium reaction in which the substrate is deprotonated at HO-2 of the glycon moiety, and at the same time assumes the *1C*(D) conformation. In this conformation, the steric requirements for operation of the anchimeric assistance of the C-2 oxyanion are fulfilled, since the C-2 oxyanion and the C-1 phenoxyl now assume a *trans*-diaxial disposition. The following reaction step (S_Ni) involves the nucleophilic attack of the C-1 of the glycon group by the C-2

oxyanion, with simultaneous release of the aglycon group and formation of an unstable intermediate (1,2-anhydroxylose), which then reacts rapidly with the hydroxide ion of the solvent. The S_Ni reaction constitutes the rate-limiting step.

This mechanism is in full accordance with the influence of the base concentration on the rate of the reaction, and with the equation (rectangular hyperbole) for the experimental pseudo-first-order rate coefficient, $k_1 = kK[\text{Base}]/(1+K[\text{Base}])$. However, in this equation, the correct measure of the influence of the base on the rate is not the concentration of the hydroxyl ions, but the proton-abstracting power of the solution, as measured by the H_- acidity function. If only this first mechanism were operative, the reaction rate should become constant at high concentrations of the base. Since this is not observed, a second mechanism, which remains dependent on $[HO^-]$ even at high concentrations of the base, must be co-operating.

This second mechanism involves the nucleophilic attack of hydroxide ion at C-1 of the aglycon, and it follows the equation $k_1 = k_2[\text{Base}]$. Again, the influence of the base has to be measured by an acidity function (J_-, or approximately H_-), and not by the stochiometric concentration of $[HO^-]$.

Since the two mechanisms operate simultaneously, the overall equation will be

$$v = k_2[K_w/h_-] + \frac{kK[K_w/h_-]}{1+K[K_w/h_-]},$$

in which K_w/h_- is a measure of the proton-abstracting power of the solution. Although this equation is only approximate (because of the necessary assumptions made in the calculation and the use of K_w/h_-), the agreement between the calculated and experimental values is more than sufficient. As a consequence of the simultaneous operation of the two mechanisms, the exact interpretation of the activation parameters becomes impossible.

When anchimeric assistance by the C-2 oxyanion is impossible (2-*O*-methyl and 2,3,4-tri-*O*-methyl derivatives), the hydrolysis proceeds by the S_N2Ar mechanism. A rough calculation shows that for *p*-nitrophenyl β-D-xylopyranoside the experimental k_1 (80°) in 0.05M sodium hydroxide must be $\sim 2\times 10^{-3}$ sec^{-1}. Consequently, this derivative is hydrolyzed 1000 times faster than the 2-*O*-methyl derivative at this temperature. The reason why the 2,3,4-tri-*O*-methyl derivative hydrolyzes 3.7 times slower than the 2-*O*-methyl compound is not known. A possible explanation might be that anchimeric assistance[11,12] of MeO-2 is still involved in the reaction. For the 2,3,4-tri-*O*-methyl derivative, the change to the *1C*(D) conformation will be energetically more unfavourable than for the 2-*O*-methyl derivative, and thus, for the latter derivative, the rate enhancement should be less. Another explanation might be that some sort of anchimeric assistance or assisted solvolysis[4] by the other (C-3 and C-4) oxyanions is possible.

The rate-limiting step of the S_Ni mechanism will be dependent on the electronic effect of the substituent on the phenyl ring. Thus, the electron-withdrawing nitro substituent will make the nitrophenol group a very good leaving-group. On the other

hand, the equilibrium constant K will be independent of the para substituent, but dependent on the structure of the glycon group, since the equilibrium also involves the conformational change.

The rate constant k_2 of the S_N2Ar mechanism will be highly dependent on the partial positive charge of C-1, and thus on the electron-withdrawing power of the substituent. With electron-donating substituents, k_2 will be very small or even negligible.

Although the S_Ni mechanism is consistent with the present experimental observations and with the influence of the base concentration on the rate, the exact nature of the intermediate and of the release of the *p*-nitrophenolate ion is not known. Thus, more-complex mechanisms[9,10] are still possible.

EXPERIMENTAL

p-Nitrophenyl β-D-xylopyranoside was prepared as described previously[18]. The 1,3,4-tri-*O*-acetyl-2-*O*-methyl-D-xylose (**1**) was prepared from 2-*O*-methyl-β-D-xylose[19] according to Fernez[20]. Treatment of **1** (10 g) with hydrobromic acid in acetic acid yielded 3,4-di-*O*-acetyl-2-*O*-methyl-α-D-xylopyranosyl bromide (**2**, 8 g), m.p. 68°. Compound **2** is very unstable and was used immediately. Reaction of **2** (8 g) with *p*-nitrophenol in a modified Michael[18,21] condensation yielded *p*-nitrophenyl 3,4-di-*O*-acetyl-2-*O*-methyl-β-D-xylopyranoside (**3**, 2 g). When purified by crystallisation from ethanol–water (3:1) at 4°, **3** had m.p. 91–92°, $[\alpha]^{22}_{5890}$ −77.6° (*c* 0.5, chloroform).

Anal. Calc. for $C_{16}H_{19}NO_9$: C, 52.0; H, 5.2. Found: C, 52.2; H, 5.1.

Deacetylation of **3** with barium methoxide[22] and recrystallisation of the product from water yielded *p*-nitrophenyl 2-*O*-methyl-β-D-xylopyranoside (95%), m.p. 133–134°, $[\alpha]^{22}_{5890}$ −56°, $[\alpha]_{5460}$ −138.4° (*c* 0.5, methanol).

Anal. Calc. for $C_{12}H_{15}NO_7$: C, 50.5; H, 5.3. Found: C, 50.0; H, 5.2.

Purdie methylation[23] of *p*-nitrophenyl β-D-xylopyranoside and crystallisation of the product from ethanol gave *p*-nitrophenyl 2,3,4-tri-*O*-methyl-β-D-xylopyranoside, m.p. 105–106°, $[\alpha]^{22}_{5890}$ −88.6°, $[\alpha]^{22}_{4360}$ −225° (*c* 0.5, chloroform).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.7; H, 6.1. Found: C, 53.5; H, 6.0.

Reaction rates at 22° were followed continuously at 400 nm with a Beckman DB-G spectrophotometer equipped with a 10-in. Lin-Log recorder and a thermostat circulator. Pseudo-first-order rate constants (k_1) were calculated by the Guggenheim[24] method, or by the log $[E_\infty - E_t]$ method.

Rates at higher temperatures were measured discontinuously. Fifteen to twenty portions of the xyloside solution in sodium hydroxide were transferred to glass-stoppered tubes, and simultaneously immersed in a thermostat bath. When they had reached thermostat temperature, the first tube was withdrawn and this time taken as zero. After measured intervals, the other tubes were withdrawn and cooled, and the *p*-nitrophenol was measured at 400 nm. The pseudo-first-order rate coefficients were calculated from least-squares, straight-line fits of the usual log plots: $\ln S_t = \ln S_0 - kt$.

Calculations of the thermodynamic activation functions were performed as described previously[25].

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